

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

TICE *et al.*

Appl. No.: 10/614,116

Filed: July 3, 2003

For: **Ketone Ligands for Modulating the  
Expression of Exogenous Genes Via  
an Ecdysone Receptor Complex**

Confirmation No.: 3335

Art Unit: 1633

Examiner: Popa, Ileana

Atty. Docket: 2584.0020001/RWE/RAS

**Declaration of Robert E. Hormann Under 37 C.F.R. § 1.132**

Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450

Sir:

I, Robert E. Hormann, declare and state as follows:

1. I received a B.A. degree in Biochemistry from Dartmouth College and a Ph.D. in Chemistry from the University of Chicago. My training continued in bioorganic chemistry at the Swiss Federal Institute of Technology. A copy of my curriculum vitae is attached as Exhibit 1.

2. I am currently employed at Intrexon Corporation (the assignee of the above-captioned application), where I hold the position of Director of Chemistry. My work includes researching and developing ecdysone receptor ligands for use in gene switch activation systems.

3. I am co-inventor of the subject matter of U.S. Application No. 10/614,116 ("the present application"), filed July 3, 2003, which is referenced above.

4. I have reviewed and am familiar with the Office Action dated November 14, 2006 ("the Office Action") and the Advisory Action dated March 26, 2007 ("the Advisory Action"), issued by the U.S. Patent and Trademark Office in the present application. I have reviewed and am familiar with Martinez *et al.*, (*Mol. Gen. Genet.*

261:546 (1999)), Dhadialla *et al.* (*Annu. Rev. Entomol.* 43:545 (1998)), Saez *et al.* (*Proc. Natl. Acad. Sci. USA* 97:14512 (2000)), Guan *et al.* (*J. Combinatorial Chem.* 2:297 (2000)), and Michelotti *et al.* (U.S. Patent No. 5,304,572), cited by the Examiner.

5. In the Office Action, the Examiner asserts one of ordinary skill in the art would have expected that the compound DTBHIB taught in Dhadialla *et al.* was capable of activating a gene switch because it has a structure similar to diacylhydrazine compounds taught in Martinez *et al.*, Saez *et al.* and Dhadialla *et al.*, some of which have been shown to function as gene switch activators, and that it would have been obvious to modify the structure of DTBHIB to produce other compounds that act as gene switch activators. The Examiner further alleges that the compounds disclosed in Michelotti *et al.* would reasonably be expected to function as gene switch activators because they are structurally similar to DTBHIB.

6. It is my opinion, based on my experience with ecdysone receptor ligands and the experimental results described below, that one of ordinary skill in the art would not have reasonably expected that DTBHIB and the compounds of Michelotti *et al.* would function as gene switch activators.

7. Exhibits 2 and 3 attached hereto describe the results of testing diacylhydrazine compounds for the ability to (a) bind to the ecdysone receptor in an intact organism and induce the natural ecdysone-responsive pathways (as evidenced by the lethal dose required to kill an insect through ecdysone receptor-mediated pathways), and (b) function as a gene switch activator in an ecdysone receptor-based system (as evidenced by induction of gene expression in a cell carrying a gene switch construct). Exhibit 2 (southern armyworm (SAW)) and Exhibit 3 (tobacco budworm (TBW)) show a plot of insect toxicity (Y-axis) against gene switch activity (X-axis). As can be seen in both plots, there is little correlation between insect toxicity (with implicit ecdysone receptor binding activity) and gene switch activity. These results strongly suggest that a compound that is able to bind the ecdysone receptor is not necessarily able to function as a gene switch activator. Likewise, some compounds that are excellent gene switch activators are only weak insecticides. Thus, the ability of a compound to bind to the

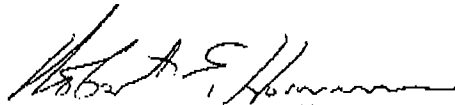
ecdysone receptor, such as is taught in Dhadialla *et al.* for DTBHIB, cannot lead one of ordinary skill in the art to expect that the compound functions as a gene switch activator as there is not enough correlation between the two activities to be predictable.

8. Exhibit 4 attached hereto describes experimental results comparing the gene switch activation potency of diacylhydrazine compounds and the same compounds missing the right-hand carbonyl group as measured by the fold induction of gene expression. Gene switch activity was tested in two different assays, 13B3 (Chinese hamster ovary cells) and Z3 (293 human embryonic kidney cells) and at two different doses, 0.33 and 33  $\mu$ M. Additionally, an  $EC_{50}$  was determined for the compounds RG-106328 and RG-100397/RG-102500. The data indicate that many of the diacylhydrazine compounds have strong gene induction activity while the corresponding compounds without the carbonyl group have essentially no gene induction activity. These results indicate that the right-hand carbonyl group is essential for gene switch activity. Importantly, the compound DTBHIB does not have a carbonyl group that corresponds to the right-hand carbonyl group of the diacylhydrazine compounds. One of ordinary skill in the art would therefore consider it likely that DTBHIB does not function as a gene switch activator.

9. Exhibit 5 attached hereto describes experimental results for gene switch activity assays of three compounds that fall within the scope of compounds described by Michelotti *et al.* (see compounds RG-108841, RG-108858, RG-109043) as well as numerous other compounds that have a similar structure in terms of a haloalkyl group at one end and an aryl group at the other end. The compounds depicted in Exhibit 5 were assayed at levels of 0.33 and 33  $\mu$ M in both 13B3 and Z3 cells. All of the tested compounds were essentially inactive in the gene switch assay. Thus, a variety of compounds encompassed by the structures taught by Michelotti *et al.* as well as compounds that are structurally similar to the compounds of Michelotti *et al.* do not have gene switch activity. These results support the position that modification of the structure of DTBHIB would not be expected to result in compounds having gene switch activity.

10. I further declare that the above statements made of my own knowledge are true and the above statements based on information and belief obtained from the references and documents discussed are believed to be true. Additionally, I declare that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Title 18 United States Code Section 1001, and that willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Respectfully submitted,



Robert E. Hormann

Date: 5-14-07

# **EXHIBIT**

**1**

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2.  
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME		POSITION TITLE	
Hormann, Robert E.		Director of Chemistry	
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Dartmouth College, Hanover, NH	B.A.	1977-81	Biochemistry
The University of Chicago	Ph.D.	1981-1987	Chemistry
Swiss Federal Inst. of Technology (E.T.H.), Zürich, Switzerland	Postdoctoral training	1987-1990	Bioorganic Chemistry

**A. Positions and Honors.**Positions and Employment

1987-1990 N.I.H. Postdoctoral Fellow, Swiss Federal Inst. of Technology  
 1990-1992 Senior Scientist, Exploratory Biocides  
 1992-1999 Senior Scientist, Exploratory Agricultural Products Research  
 1999-2003 Chemistry Program Leader, RHeoGene (Rohm and Haas Company)  
 2003-present Director of Chemistry, RheoGene, Inc.

Other Experience and Professional Memberships

1982-present Member, American Chemical Society  
 2006 16th International Ecdysone Workshop, Ghent Belgium, 2006. Program Committee  
 2006 7th International Workshop on the Molecular Biology and Genetics of the Lepidoptera, Kolympari, Crete, Greece, 2006. Program Committee

Honors

1977-1981 Rufus Choate Scholar, Dartmouth College  
 1981 Summa Cum Laude, Dartmouth College  
 1981-1982 Morris Kharasch Fellow, The University of Chicago  
 1983-1987 N.I.H. Pharmacology Training Program, The University of Chicago  
 1988-1989 N.I.H. Postdoctoral Fellowship, Swiss Federal Institute of Technology  
 1997 Otto Haas Award for Technical Excellence, Rohm and Haas Company

**B. Selected peer-reviewed publications (in chronological order).**Publications

1. Gross, R. H., Hormann, R. E., Saxe, J., Purification and Partial Characterization of Virus-Like Particles from Schneider Line 2 Drosophila Cells, *Arch. Biochem. Biophys.*, 1981, 207(2), 455-9.
2. Eaton, P. E., Hormann, R. E., Azidocubanes. 1. Photolysis: Formation of a Homoprismyl Nitrile. *J. Am. Chem. Soc.*, 1987, 109(4), 1268-9.
3. Eaton, P. E., Fisher, A. M., Hormann, R. E., Azidocubanes. 2. Acid-Induced Rearrangement: Formation of 9-Azahomocubanes, *Synlett*, 1990, 12, 737-8.
4. Giner, J.-L., Hormann, R., Arigoni, D., Multiply Labeled Substrates as Tools for the Study of an Unusual Biomethylation Reaction, *Synth. Appl. Isot. Labelled Compd.* 1994, 5th Proc. Int. Symp., 1995, 723-6.
5. Reynolds, C. H., Hormann, R. E., Theoretical Study of the Structure and Rotational Flexibility of Diacylhydrazines: Implications for the Structure of Nonsteroidal Ecdysone Agonists and Azapeptides, *J. Am. Chem. Soc.*, 1996, 118 (39), 9395-9401.
6. Hormann, R. E., Nonnatural Products Nonpareil, *Aldrichimica Acta*, 1996, 29(2), 31-39. Dinan, L., Hormann, R. E., Fujimoto, T., An Extensive Ecdysteroid CoMFA, *J. Comput.-Aided Mol. Des.*, 1999, 13(2), 185-207.
7. Ravi, M., Hopfinger, A. J., Hormann, R. E., Dinan, L., 4D-QSAR Analysis of a Set of Ecdysteroids and a Comparison to CoMFA Modeling, *J. Chem. Info. Comp. Sci.*, 2001, 41(6), 1587-1604.
8. Bourne, P. C., Whiting, P., Dhadialla, T. S., Hormann, R., Girault, J.-P., Harmatha, J., Lafont, R., Dinan, L., Ecdysteroid 7,9(11)-Dien-6-ones as Potential Photoaffinity Labels for Ecdysteroid Binding Proteins, *J. Insect Sci.*, 2002, 2(11), 11 pp., [www.insectscience.org/2.11](http://www.insectscience.org/2.11).
9. Dinan L., Bourne P., Whiting P., Tsitseklis A., Saatov Z., Dhadialla T.S., Hormann R.E., Lafont R., Coll J., Synthesis and Biological Activities of Turkesterone 11- $\alpha$ -acyl derivatives, *Journal of Insect Science*, 2003, 3(6), 11 pp., [www.insectscience.org/3.6](http://www.insectscience.org/3.6).
10. Tice, C. M., Hormann, R. E., Thompson, C. S., Friz, J. L., Cavanaugh, C. K., Michelotti, E. L., Garcia, J., Nicolasc, E., Albericio, F., Synthesis and SAR of Alpha-Acylaminoketone Ligands for Control of Gene Expression, *Bioorganic & Medicinal Chemistry Letters*, 2003, 13, 475-478.
11. Hormann, R., Dinan, L., Whiting, P., Superimposition evaluation of ecdysteroid agonist chemotypes through multidimensional QSAR, *Journal of Computer-Aided Molecular Design*, 2003, 17, 135-153.
12. Tice, C. M.; Hormann, R. E.; Thompson, C. S.; Friz, J. L.; Cavanaugh, C. K.; Saggars, J. A., Optimization of  $\alpha$ -acylaminoketone ecdysone agonists for control of gene expression. *Bioorganic & Medicinal Chemistry Letters*, 2003, 13, 1883-1886.
13. Kumar, M.B., Potter, D.W., Hormann, R.E., Edwards, A., Tice, C.M., Smith, H.C., Dipietro, M.A., Polley, M., Lawless, M., Wolohan, P.R.N., Kethidi, D.R., and Palli, S.R. Highly Flexible Ligand Binding Pocket of Ecdysone Receptor, *M., J. Biol. Chemistry*, 2004, 279:26, 27211-27218.
14. L Dinan, R E Hormann, Ecdysteroid Agonists and Antagonists, in *Comprehensive Molecular Insect Science*, L.I. Gilbert, ed., 2005.
15. Palli,S., Hormann, R.E., Schlattner, U., Lezzi, M., Ecdysteroid Receptors and Their Applications in Agriculture and Medicine, in *Insect Hormones*, Volume 73 of *Vitamins and Hormones*, Gerald Litwack, Ed. -. Pp. 60-91, 2005.
16. Schlattner, U., Vafopoulou, X., Steel, C.G.H., Hormann, R.E., Markus Lezzi, Non-genomic ecdysone effects and the invertebrate nuclear steroid hormone receptor EcR—new role for an “old” receptor?, *Molecular and Cellular Endocrinology*, 2006, in press.
17. Garcia, J., Mata, E., Tice, C., Hormann, R. E. Ernesto, N., Albericio, F., Michelotti, E., Evaluation of Solution and Solid-Phase Approaches to the Synthesis of Libraries of  $\alpha,\alpha$ -Disubstituted- $\alpha$ -acylaminoketones, *Journal of Combinatorial Chemistry*, 2005, 7, 843-863.

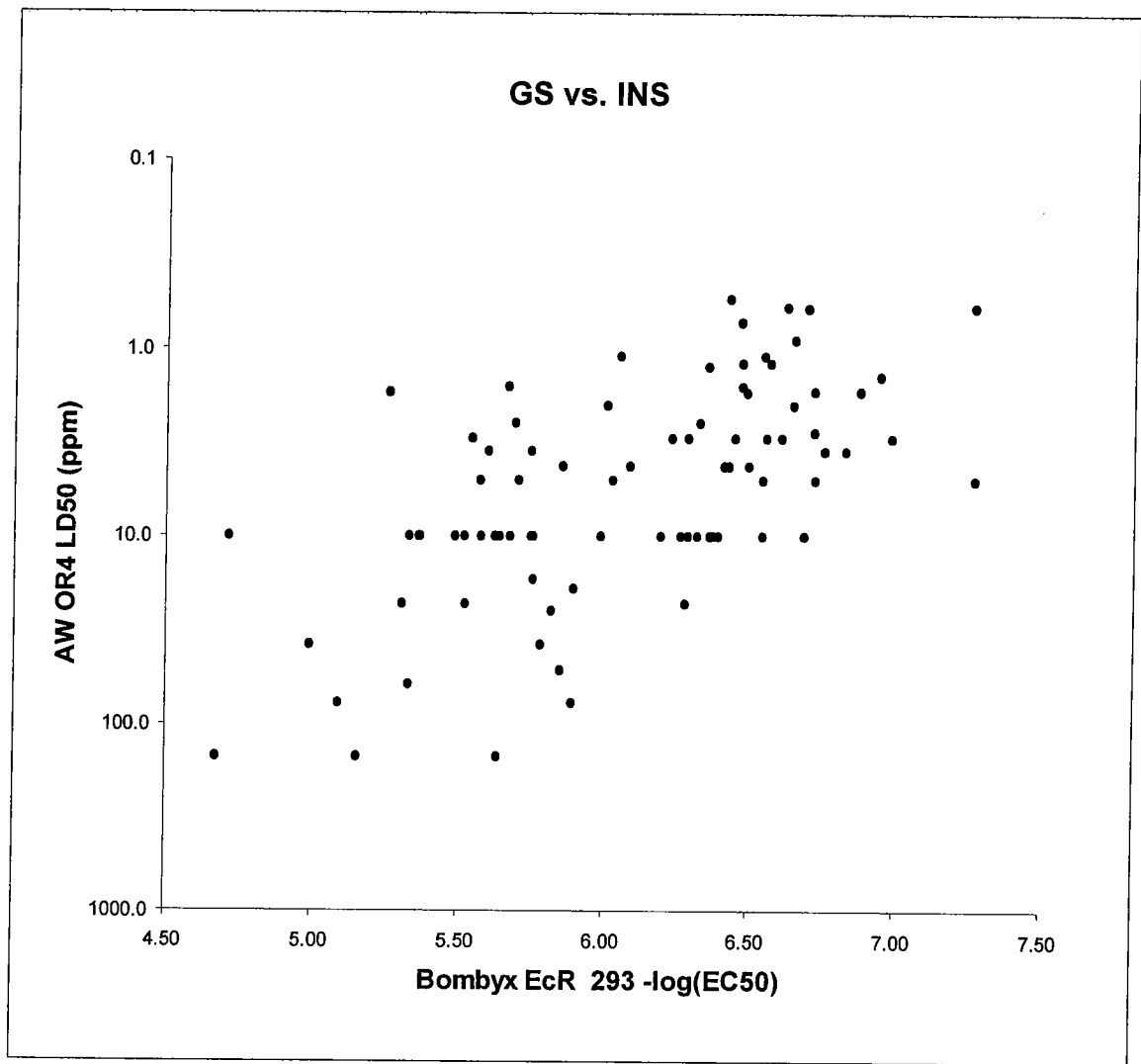
Patents and Patent Applications

1. Hormann, R. E., Insecticidal N,N'-Disubstituted-N,N'-Diacylhydrazines, 1996, U.S. 5,482,962 A.  
Lidert, Z., Le, D. P., Hormann, R. E., Opie, T. R., Insecticidal N'-Substituted-N,N'-Diacylhydrazines, 1996, C.I.P. of U.S. 5, 344, 958, U.S. 5,530,028.
2. Hormann, R. E., Preparation of Chromancarboxylates, 1997, E.P. 773,216 A.
3. Hormann, R. E., Preparation of Chroman-6-carboxylates, 1997, U.S. 5,698,716 A.
4. Hormann, R. E., Preparation of Intermediates for Chromancarboxylates, 1998, C.I.P. of U.S. 5,698,716.
5. Hormann, R. E., Gilbert, D. E., Sioma, E. M., Apparatus and Method Used in Multiple, Simultaneous Synthesis of General Compounds, 2001, U.S. 6,258,323.
6. Carlson, G. R., Cress, D. E., Dhadialla, T. S., Hormann, R. E., Le, D. P., Ligands for Modulating the Expression of Exogenous Genes Via an Ecdysone Receptor Complex, 2001, US 6,258,603.
7. Dhadialla, T. S., Cress, D. E., Carlson, G. R., Hormann, R. E., Palli, S. R., Kudla, A. J., Herzig, R. P. Jr., Philip, M., Ecdysone Receptor, Retinoid X Receptor and Ultraspiracle Protein Based Dual Switch Inducible Gene Expression Modulation System, 2002, WO-0229075 A2.
8. Tice, C.M.; Michelotti, E.L., Hormann R.E., Ketone ligands for Modulating the Expression of Exogenous Genes via an Ecdysone Receptor Complex, 2004, US-2004-0049037.
9. Hormann, R.E.; Potter, D. W.; Chortyk, O.; Tice, C. M.; Carlson, G.R.; Meyer, A.; Opie, T. R., Diacylhydrazine ligands for modulating expression of transgenes via chimeric ecdysone receptor complexes, 2004, WO 2004078924.
10. Hormann, R.E.; Chortyk, O.; Le D.P., Oxadiazoline ligands as non-steroidal ligands for ecdysone receptors and their use in modulating genes regulated by the receptor, 2004, US 2004171651 A1.
11. Hormann, R.E.; Tice, C. M.; Chortyk, O.; Smith, H.; Meteyer, T. Diacylhydrazine ligands for modulating the expression of exogenous genes in mammalian or plant cells with ecdysone receptor complexes, 2004, WO 2004072254 A2.

# **EXHIBIT**

**2**

# SAW



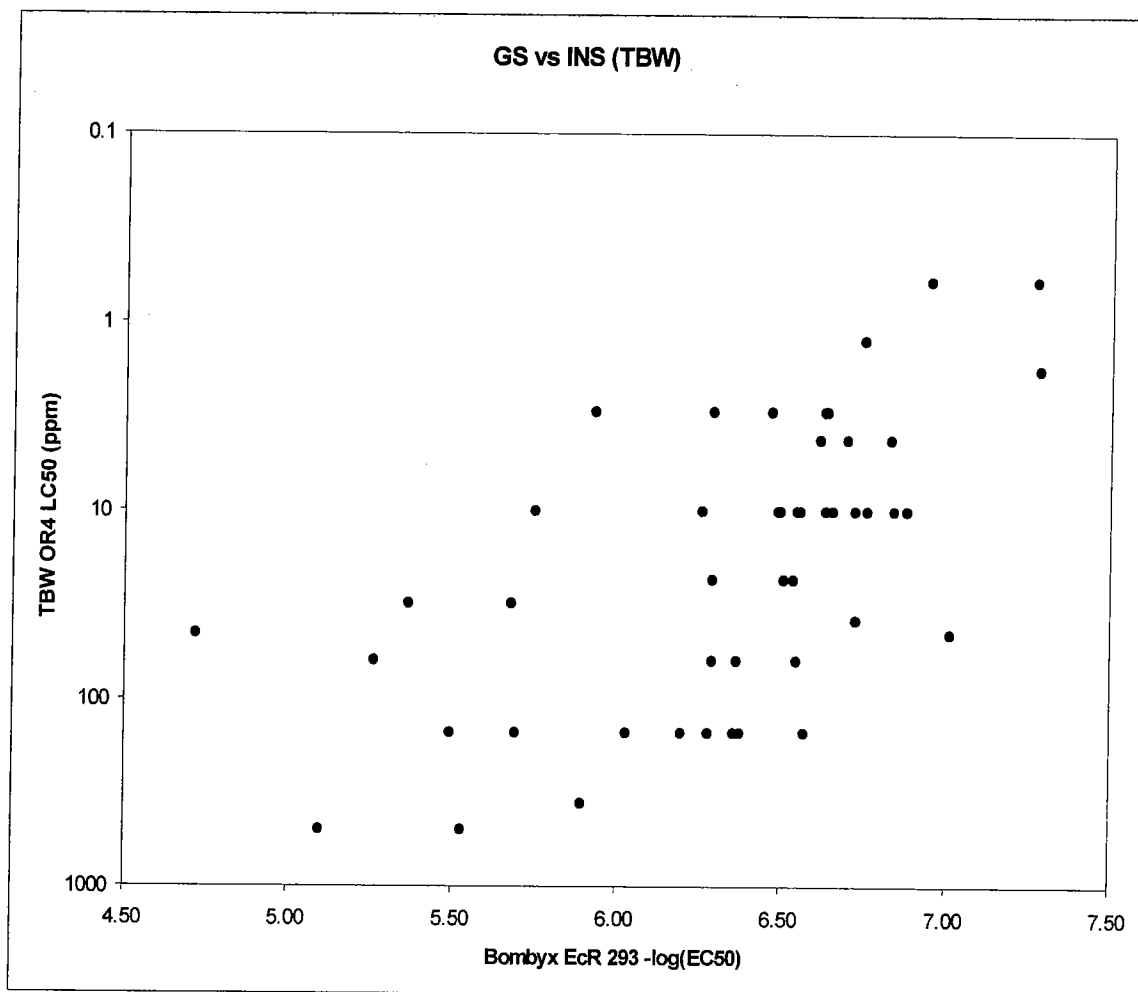
Correlations		
-LOG(LC50)	AW OR4	-0.534
-LOG(LC50)	-log(AW OR4)	0.647
LC50	AW OR4	0.792
Max Cmp / Max GSE	AW OR4	-0.045

n = 85

# **EXHIBIT**

**3**

# TBW



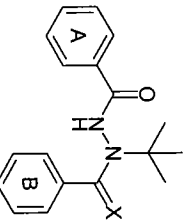
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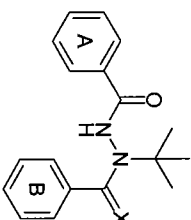
-LOG(LC50)	AW OR4	-0.522
-LOG(LC50)	-log(TBW OR4)	0.606
LC50	AW OR4	0.281
Max Cmp / Max GSE	AW OR4	-0.48

n = 48

# **EXHIBIT**

**4**

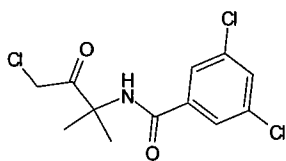
<div></div>				Fold Induction							
				X = H,H				X = C=O			
				13B3 (μM)				13B3 (μM)			
				Z3 (μM)				Z3 (μM)			
A-RING	B-RING	X = H,H	X = (C=O)	0.33	33	0.33	33	0.33	33	0.33	33
H	H	RG-106328	RG-100397 / RG-102500	0.7	0.3	1.6	3.7	1.0	40.3	1.5	691.3
H	2-CH3	RG-104839	RG-100453	1.0	0.6	1.1	3.5	0.8	140.3	68.8	103.6
H	2-Br	RG-105624	RG-101031	2.6	0.5	1.3	24.9	1.2	1.2	1.0	1.6
H	2-NO2	RG-104401	RG-100296	1.0	0.6	1.3	2.3	1.0	411.2	1.1	0.9
H	3-CH3	RG-105827	RG-100783	0.8	0.3	1.4	1.1	0.9	573.1	1.7	145.3
H	3-CF3	RG-105919	RG-101081	1.2	0.8		1.8	0.9	1.3	0.9	3.3
H	3-NO2	RG-105635	RG-100295	1.3	1.1	1.2	5.5	0.8	1.3	1.5	2.0
H	3-OCH3	RG-106046	RG-100452	0.9	1.0		1.3	0.9	5.8	1.1	73.7
H	4-CH3	RG-106633	RG-100782	0.7	0.9	1.3	1.3	0.8	0.6	1.2	13.9
H	4-OCH3	RG-104448	RG-100451	2.3	0.3		1.0	0.9	1.2	0.9	1.4
H	4-F	RG-103735	RG-100537	1.4	1.4	0.7	5.0	0.9	8.8	1.3	34.5
H	2,4-di-Cl	RG-106223	RG-101320	1.9	0.6		2.3	0.7	501.5	7.1	257.5
H	3,4-diCl	RG-103406	RG-101321	1.6	0.4		3.1	0.7	16.0	1.8	93.1
4-CH3	H	RG-106632	RG-100781	1.0	0.9	1.1	1.5	0.9	1209.1	26.9	328.4
4-CH3	3-CH3	RG-104782	RG-101189	0.5	0.0	1.1	0.8	0.8	573.4	24.2	256.3
4-CH3	4-CH3	RG-105971	RG-101186	1.2	0.0	1.4	1.1	0.9	1166.1	1.4	11.4
3,4-di-Cl	H	RG-104515	RG-101325	0.7	0.5		2.2	0.6	0.6	0.8	14.8

<div></div>				EC50 , relative maximum fold induction							
				X = H,H				X = C=O			
				13B3				13B3			
				Z3				Z3			
A-RING	B-RING	H,H	C=O	EC50 (μM)	RMFI	EC50 (μM)	RMFI	EC50 (μM)	RMFI		
H	H	RG-106328	RG-100397 / RG-102500	See above (inactive)				41.5	(0.03)	31.5	(0.6)

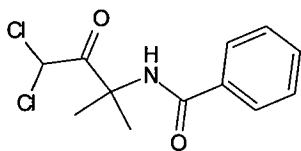
# **EXHIBIT**

## **5**

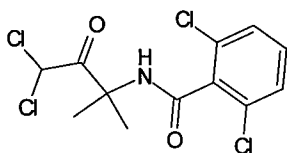
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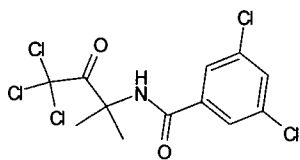
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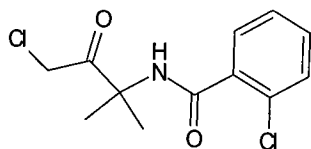
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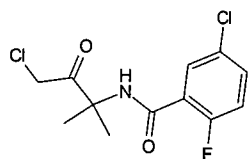
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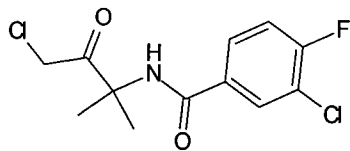
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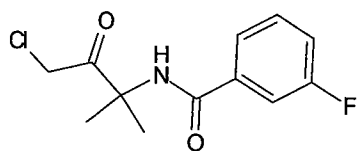
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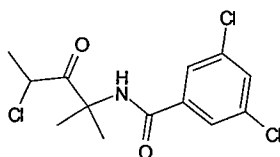
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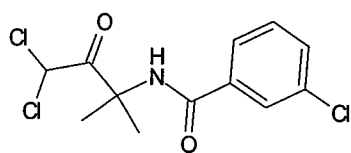
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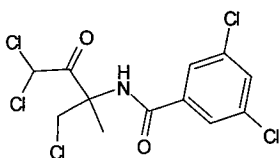
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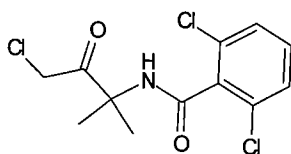
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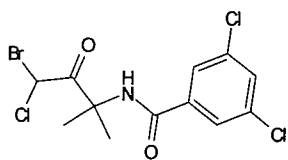
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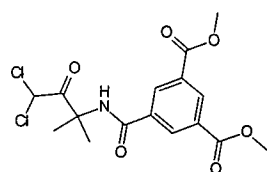
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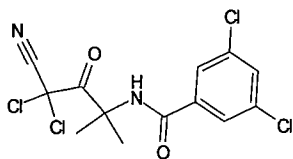
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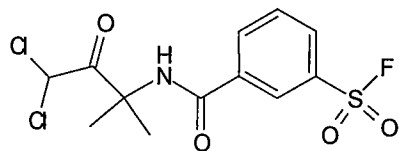
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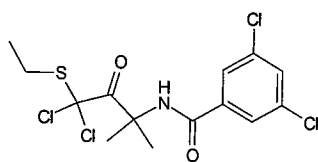
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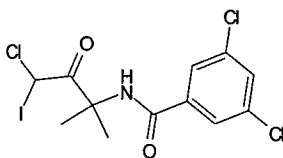
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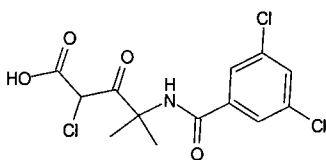
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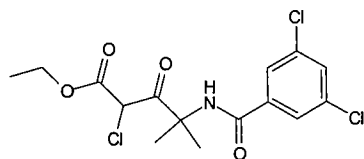
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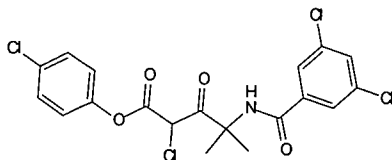
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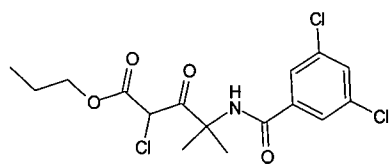
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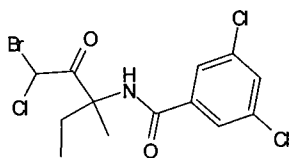
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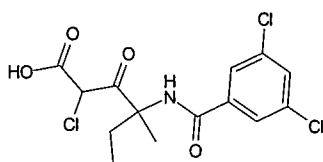
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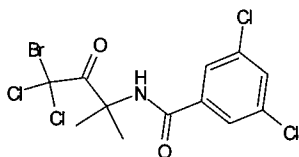
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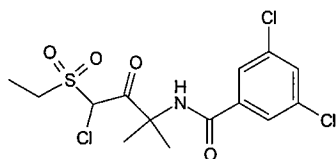
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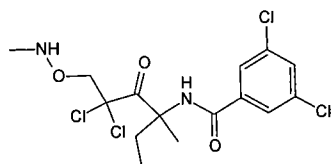
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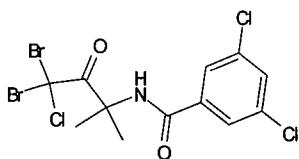
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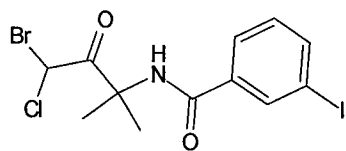
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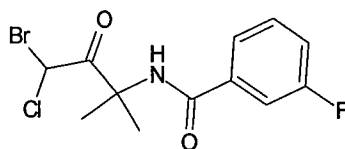
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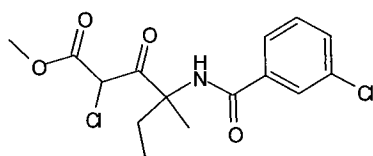
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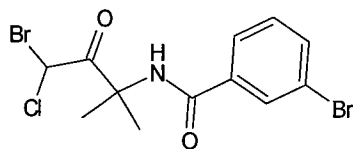
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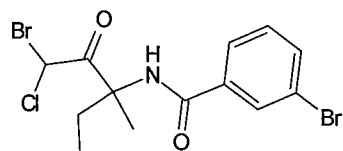
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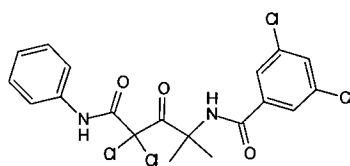
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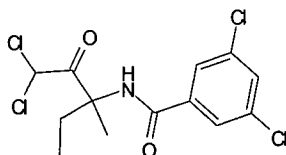
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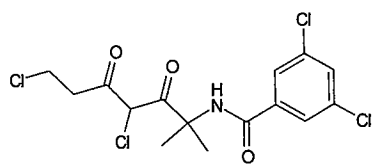
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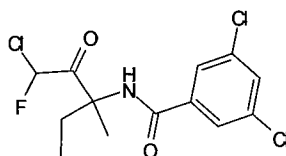
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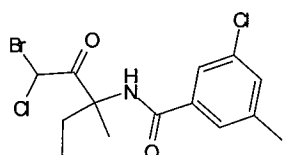
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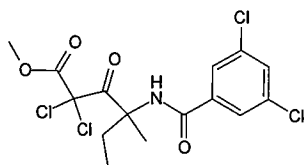
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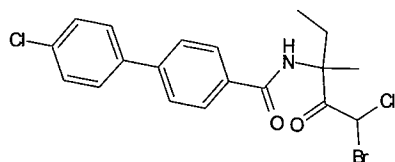
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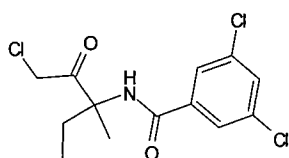
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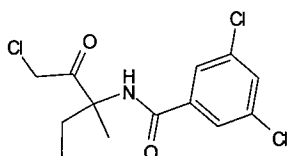
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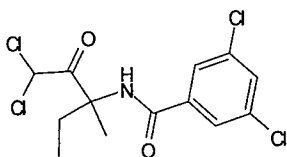
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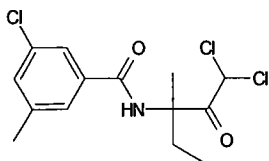
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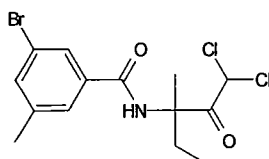
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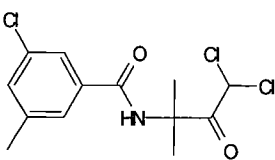
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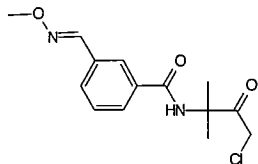
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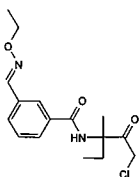
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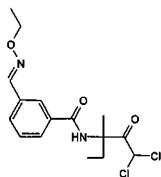
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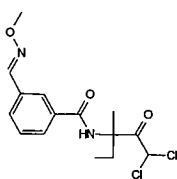
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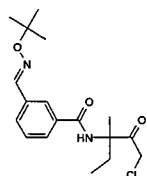
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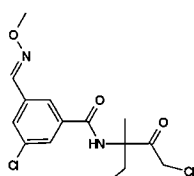
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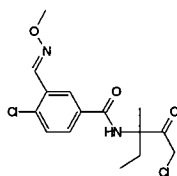
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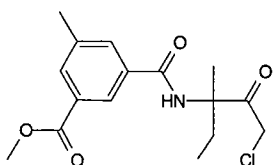
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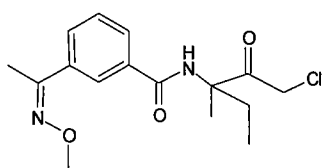
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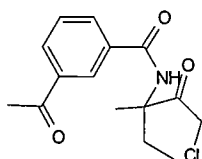
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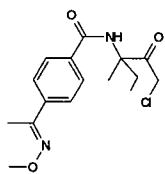
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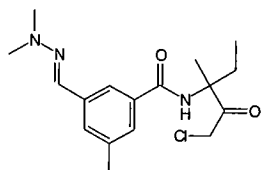
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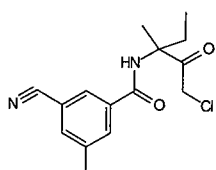
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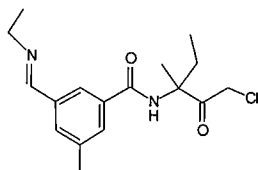
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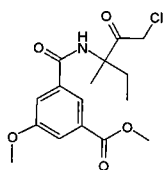
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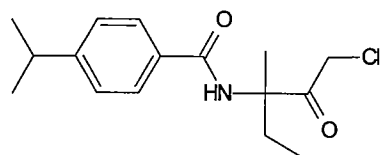
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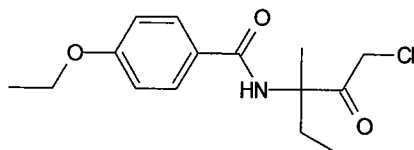
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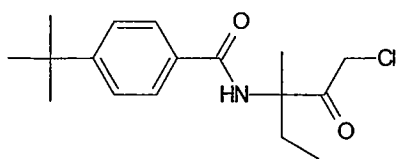
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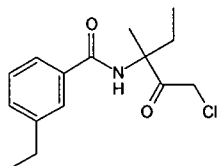
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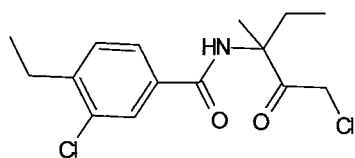
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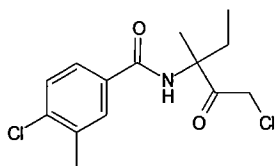
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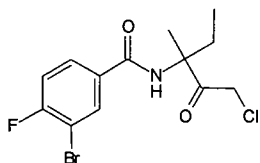
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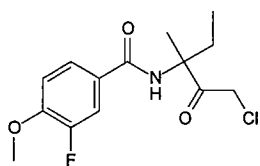
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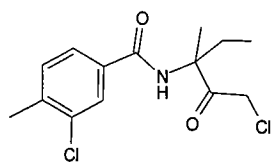
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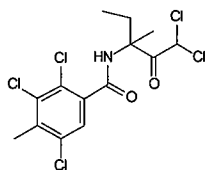
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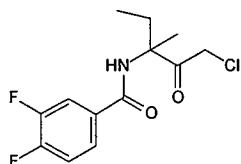
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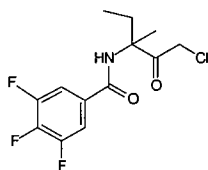
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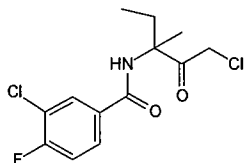
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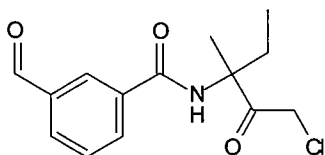
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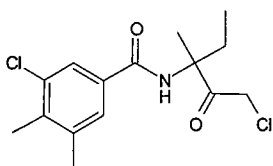
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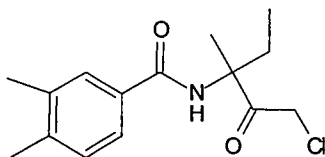
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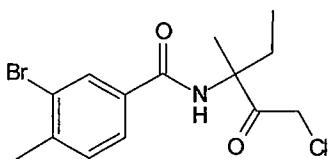
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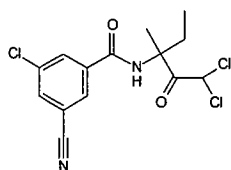
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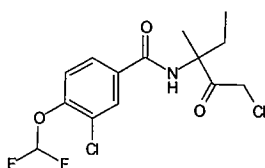
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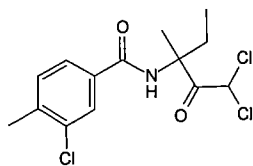
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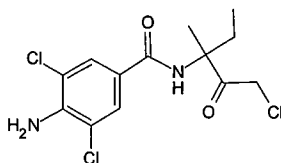
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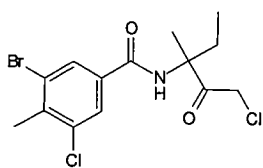
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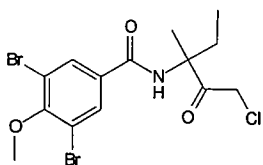
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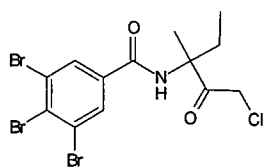
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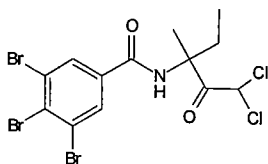
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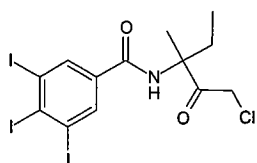
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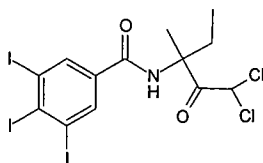
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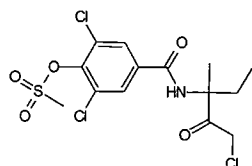
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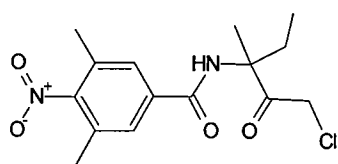
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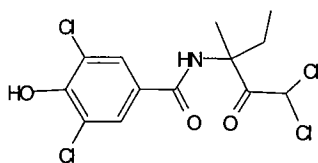
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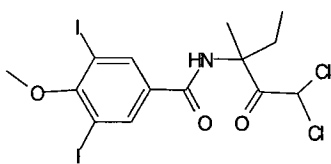
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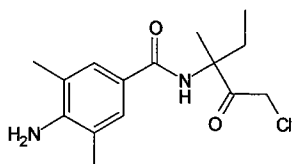
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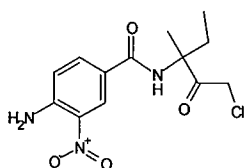
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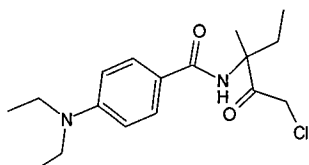
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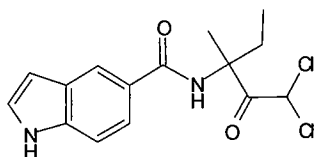
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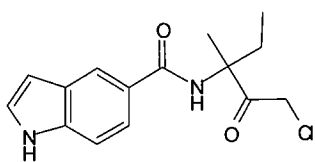
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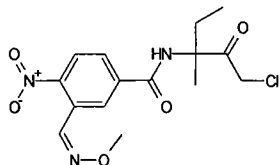
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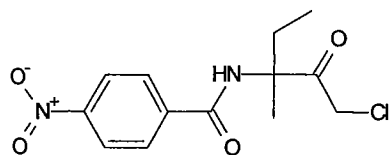
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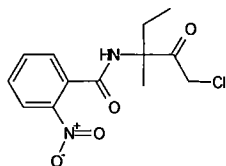
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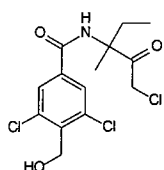
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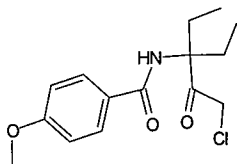
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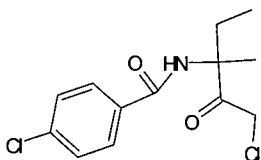
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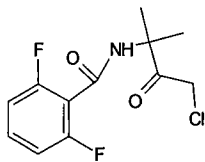
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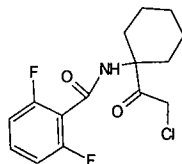
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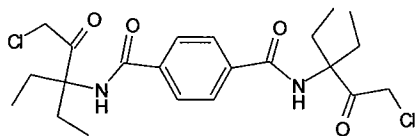
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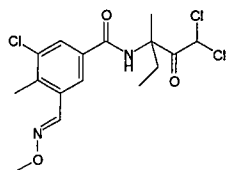
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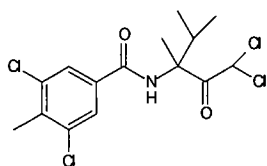
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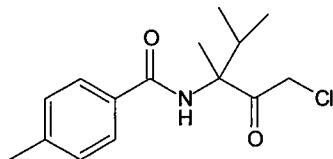
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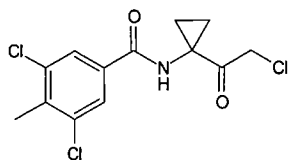
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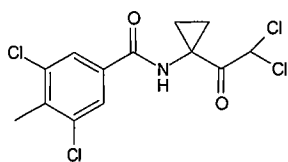
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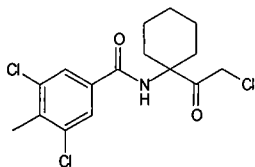
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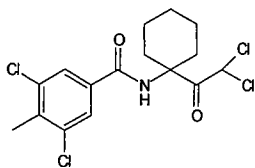
RG-108848



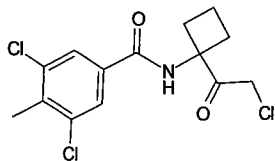
RG-108809



RG-109076



RG-108808



RG-108804

## 13B3 Assay

concentration in micromolar

Average of Result Value	Concentration	
Corporate ID	0.330	33.000
RG-108801	0.850	0.250
RG-108804	1.200	2.500
RG-108806	0.800	0.000
RG-108808	1.800	0.000
RG-108809	0.600	0.000
RG-108811	0.000	0.000
RG-108813	0.000	0.000
RG-108814	0.000	0.000
RG-108815	0.000	0.000
RG-108817	4.000	0.000
RG-108819	0.000	0.000
RG-108825	0.000	0.000
RG-108837	0.000	0.000
RG-108839	0.000	0.000
RG-108841	0.000	0.000
RG-108842	0.000	0.000
RG-108848	3.000	0.000
RG-108853	0.000	0.000
RG-108854	0.000	0.000
RG-108855	0.000	0.000
RG-108858	0.000	0.000
RG-108860	0.000	0.000
RG-108862	1.600	1.000
RG-108864	0.000	0.000
RG-108876	0.000	0.000
RG-108880	0.500	0.000
RG-108881	1.600	0.000
RG-108882	0.000	0.000
RG-108890	0.800	0.000
RG-108895	0.000	0.000
RG-108897	0.000	0.000
RG-108902	0.000	0.000
RG-108907	0.000	0.000
RG-108908	0.700	0.000
RG-108910	0.000	0.000
RG-108919	0.000	0.000
RG-108920	0.000	0.000
RG-108921	0.000	2.500
RG-108924	0.000	0.000
RG-108927	3.500	37.000
RG-108928	0.000	1.000
RG-108932	0.000	0.000
RG-108933	0.000	0.000
RG-108937	0.000	0.000
RG-108948	0.000	0.000
RG-108952	2.333	1.600
RG-108954	0.000	0.000
RG-108955	0.000	0.000

RG-108956	0.000	0.000
RG-108965	0.000	30.000
RG-108973	0.000	0.000
RG-108984	0.000	0.000
RG-108985	0.000	0.000
RG-108991	0.000	0.500
RG-108992	1.125	0.000
RG-108996	4.000	1.400
RG-108999	0.000	0.000
RG-109005	7.800	0.000
RG-109006	0.000	0.000
RG-109007	0.000	0.000
RG-109009	8.400	0.000
RG-109010	0.000	0.000
RG-109032	7.875	0.000
RG-109040	1.800	15.000
RG-109041	2.250	0.000
RG-109043	1.500	0.000
RG-109044	0.000	0.000
RG-109056	0.000	19.000
RG-109063	0.000	0.000
RG-109065	0.000	0.000
RG-109074	0.000	0.000
RG-109076	0.700	0.000
RG-109078	0.000	9.500
RG-109079	0.000	0.000
RG-109083	0.000	0.000
RG-109089	0.000	0.000
RG-109091	10.125	0.000
RG-109095	0.000	0.000
RG-109107	0.000	0.000
RG-109112	0.000	0.000
RG-109113	0.000	0.000
RG-109119	0.000	0.000
RG-109120	7.500	0.000
RG-109124	0.000	0.000
RG-109125	2.333	2.700
RG-109127	0.000	0.000
RG-109131	0.000	0.000
RG-109135	2.200	0.000
RG-109139	0.000	0.000
RG-109141	0.000	0.000
RG-109145	0.000	0.000
RG-109162	5.625	0.000
RG-109164	0.000	0.000
RG-109165	0.000	0.000
RG-109166	7.500	0.000
RG-109170	0.000	0.000
RG-109173	0.300	0.000
RG-109174	0.000	0.000
RG-109179	0.000	0.000
RG-109180	0.000	0.000

RG-109182	0.000	0.000
RG-109191	3.800	11.000
RG-109195	0.000	0.000
RG-109198	0.000	0.000
RG-109200	0.000	1.500
RG-109204	0.000	0.000
RG-109206	0.000	0.000
RG-109207	0.000	0.400
RG-109224	0.000	0.000
RG-109228	0.000	0.000
RG-109229	0.000	0.000
RG-109240	0.000	0.000
RG-109249	4.500	0.000
RG-109259	1.167	0.000

## Z3 Assay

concentration in micromolar

Average of Result Value	Concentration	
Corporate ID	0.330	33.000
RG-108839	0.839	0.215
RG-108853	0.995	0.493
RG-108855	0.946	0.206
RG-108860	0.912	0.202
RG-108876	0.943	0.322
RG-108880	1.052	0.169
RG-108882	0.774	0.191
RG-108897	1.153	0.842
RG-108907	1.156	0.335
RG-108910	1.006	0.219
RG-108919	1.105	0.046
RG-108921	0.734	0.172
RG-108924	1.188	0.268
RG-108927	0.781	0.966
RG-108928	0.730	0.304
RG-108933	0.872	0.428
RG-108937	0.969	0.205
RG-108948	0.937	0.783
RG-108952	1.124	1.092
RG-108955	0.803	1.057
RG-108965	0.843	0.834
RG-108973	0.940	0.805
RG-108984	0.989	0.092
RG-108991	0.889	0.215
RG-108992	1.096	0.544
RG-108996	1.183	0.878
RG-108999	1.127	1.089
RG-109005	1.070	0.385
RG-109006	1.027	0.650
RG-109007	1.051	0.499
RG-109010	0.966	0.509
RG-109032	1.245	0.779
RG-109041	1.049	0.527
RG-109044	1.144	0.060
RG-109056	0.856	0.899
RG-109063	1.070	0.216
RG-109065	0.826	0.202
RG-109074	1.067	0.204
RG-109078	0.924	0.872
RG-109079	0.752	1.062
RG-109083	1.029	0.292
RG-109089	0.864	0.278
RG-109091	1.101	0.244
RG-109095	1.129	0.380
RG-109112	1.032	0.252
RG-109120	0.869	0.862
RG-109124	0.936	0.221
RG-109125	0.984	0.338

RG-109131	1.098	0.737
RG-109141	1.163	0.239
RG-109145	0.913	0.050
RG-109162	1.145	0.116
RG-109164	1.033	0.968
RG-109165	0.966	0.627
RG-109166	1.244	0.879
RG-109170	0.863	0.741
RG-109174	0.863	0.621
RG-109179	0.997	0.374
RG-109180	0.871	0.256
RG-109182	0.928	0.563
RG-109195	1.225	0.362
RG-109198	0.954	0.940
RG-109200	1.113	1.023
RG-109204	1.298	0.318
RG-109206	0.932	0.267
RG-109207	1.070	0.742
RG-109224	0.895	0.130
RG-109228	1.130	0.172
RG-109229	0.902	0.878
RG-109240	1.092	0.361
RG-109249	1.308	1.059
RG-109259	0.972	0.187

# 13B3 & Z3 EC50

Corporate ID	Assay	EC50 (uM)	Rel Max FI
RG-109056	13B3	0.369	0.002
RG-108965	13B3	>50	0.048
RG-108927	13B3	0.369	0.003
RG-109056	Z3	>50	0.002
RG-108965	Z3	>50	0.012
RG-108927	Z3	>50	0.101